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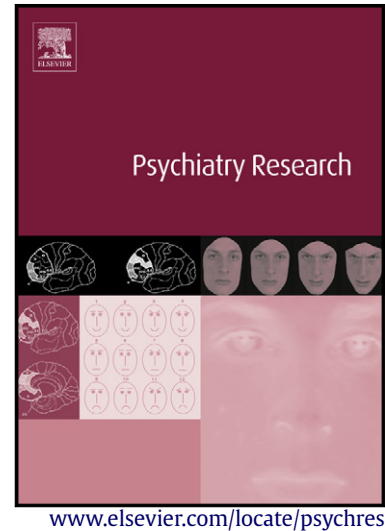
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PSYCHIATRY RESEARCH

Metabolic syndrome and lung function in schizophrenia: a pilot study

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Abstract

This pilot study aimed to explore relationships between metabolic and lung functions in patients with schizophrenia. Eighty patients with schizophrenia (55♂; 36.8±10.0 years) underwent a spirometry, were screened for metabolic syndrome (MetS), performed a 6-minute walk test (6MWT), and completed the International Physical Activity Questionnaire and the Psychosis evaluation tool for common use by caregivers. Patients with MetS (according to the International Diabetes Federation criteria) (n=28; 35%) had a reduced predicted forced expiratory volume for 1 second (77.4±13.2 versus 87.3±12.1%) and predicted forced vital capacity (75.3±11.1 versus 85.4±11.4%). Significantly more patients with MetS were diagnosed with restrictive lung dysfunction (RLD) (according to the Global Initiative for Chronic Obstructive Lung Disease criteria) (13 versus 8). Schizophrenia patients with RLD (n=21; 26.2%) had a significantly larger waist circumference (90.7±12.5 versus, 105.6±14.7cm), were less physically active (653.6±777.9 versus 1517.9±1248.7 metabolic equivalent-min/week) and walked less on the 6MWT (502.6±92.3 versus 612.4±101.2m) than patients without RLD. The present data suggest that in patients with schizophrenia RLD might be associated with metabolic dysfunctions. Further prospective analyses are required to elucidate the complex interrelationships between lung and metabolic functions in patients with schizophrenia.

Keywords: spirometry; metabolic syndrome; physical activity; exercise; physical fitness; psychosis

1. Introduction

Both in the general population (Hole et al., 1996; Sin et al., 2005) and also in patients with schizophrenia, an impaired lung function is associated with higher cardiovascular risk and increased mortality (Himelhoch et al., 2004; Hoang et al., 2011; Martens et al., 2013). Impaired lung function is a generic term that includes two different spirometric patterns, obstructive lung dysfunction and restrictive lung dysfunction (Mannino et al., 2003a, 2005). Obstructive lung dysfunction is diagnosed in the presence of a forced expiratory volume for 1 second / forced vital capacity (FEV1/FVC) ratio below 0.70, and classified according to FEV1 expressed as percent of the predicted value (FEV1%) (GOLD, 2013). Conversely, restrictive lung dysfunction is characterized by a proportionally comparable decrease of both FEV1% and FVC expressed as percent of the predicted value (FVC%), consequently resulting in a normal FEV1/FVC ratio (Mannino et al., 2003a, 2005).

Patients with schizophrenia are at an increased risk for obstructive and restrictive lung diseases (De Hert et al., 2011). For instance, the prevalence of restrictive lung disease may be present in up to half of individuals with schizophrenia (Aggarwal, 2012). However, currently the mechanisms that underlie the association between impaired lung function and increased cardio-metabolic mortality are largely unknown and they cannot be solely explained by the effects of smoking (Copeland et al., 2007; De Hert et al., 2011; Ozbulut et al., 2013). There is rigorous evidence in the general population that poor lung function is associated with insulin resistance and metabolic diseases (Ford & Mannino, 2004; Lin et al., 2006; Scarlata et al., 2010, 2013). This is an important consideration for first-episode and multi-episode patients with schizophrenia, given that they have an increased risk of the metabolic syndrome (MetS) (Vancampfort et al., 2013a; Mitchell et al., 2013a & b).

The mechanisms underlying any possible associations between lung function and metabolic risks are likely to be complex but warrant investigation. This may however include

mechanical effects of central adiposity on lung function (Lessard et al., 2011), as well as inflammatory processes (Wannamethee et al., 2010) and unhealthy lifestyle factors (e.g. smoking and a sedentary lifestyle) (Vancampfort et al., 2013b) affecting both lung function and metabolic disease risk. To the best of our knowledge, no research has been conducted so far to examine whether patients with schizophrenia who have MetS are at an increased risk for obstructive and restrictive lung dysfunctions. It is also unclear whether, in the opposite way, there is a difference in metabolic profile between schizophrenia patients with and without lung dysfunctions. Therefore, the aim of this pilot study was to explore the relationships between metabolic and lung functions in patients with schizophrenia.

2. Methods

2.1. *Participants and procedure*

Over a 6-month period, 100 in- and outpatients with a DSM-IV diagnosis of schizophrenia of the UPC KULeuven, campus Kortenberg and the Brussels Nighthospital Belgium were screened for participation. Six persons with co-morbid substance abuse were excluded while another six patients were excluded for a cardiovascular, locomotor or endocrine disorder that could prevent safe participation in a physical fitness test. Of the 88 eligible patients, another 8 declined to participate. All participants were Caucasians.

2.2. *Demographical and anthropometric data*

The demographic data were obtained from medical records. All participants were asked whether they currently smoked. Those participants who responded affirmatively to this question were asked how many cigarettes they smoked per day.

Body weight was measured in light clothing to the nearest 0.1kg using a SECA beam balance scale, and height to the nearest 0.1cm using a wall-mounted stadiometer.

2.3. *Spirometry*

Measurements of forced expiratory volume in 1sec (FEV1) and forced vital capacity (FVC) were obtained using spirometry (Micro, Cardinal Health, Chatham, UK) and following the American Thoracic Society guidelines (American Thoracic Society, 1995). Each participant completed two spirometry attempts while seated. Where the two readings differed by over 100ml, a third measurement was taken. The tests were conducted by specially trained technicians. Values used in this analysis included the FVC, the FEV1, and the FEV1/FVC ratio. Predicted values of FEV1 and FVC were determined using the normative reference equations for non-smoking Caucasians from Hankinson et al. (1999). Using the percentage of

predicted FEV₁, percentage of predicted FVC, and the FEV₁-to-FVC ratio, we followed the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (2013) to classify participants as having chronic obstructive pulmonary disease (COPD). Participants were diagnosed with COPD if they had a FEV₁-to-FVC ratio <0.70. Because too few participants were diagnosed with COPD (n=3), we were not able to divide them into categories of mild, moderate or severe COPD. In addition, we assigned participants as having restrictive lung disease (RLD) (FEV₁-to-FVC ratio ≥0.70 and FVC <80% predicted). As per GOLD (2013) criteria, we assigned participants who met the criteria for having both COPD and RLD to the COPD group.

2.4. Metabolic syndrome

All participants received a comprehensive metabolic screening including a 2-hour 75-g glucose load oral glucose tolerance test (OGTT) (De Hert et al., 2006; van Winkel et al., 2006). Patients were initiated on an overnight fast and were monitored during the OGTT. Waist circumference (WC) was measured to the nearest 1cm at the level of the umbilicus and at the end of expiration with the participant upright and his/her hands by their side. Blood pressure was recorded twice in the sitting position after a five minute rest with an Omron M6 (HEM-7001-E) (Omron® Healthcare Europe). The presence of MetS was assessed using the International Diabetes Federation criteria (Alberti et al., 2006).

2.5. Physical fitness assessment

Physical fitness was measured using the 6-minute walk test (6MWT) and according to the American Thoracic Society guidelines (American Thoracic Society, 2002) in an indoor corridor with a minimum of external stimuli. Two cones, 25m apart, indicated the length of the walkway. Participants were instructed to walk (without running or jogging) back and forth

around the cones for a total duration of six minutes. Resting was allowed if necessary, but walking was to be resumed as soon as the participants were able to do so. The protocol stated that the testing was to be interrupted if threatening symptoms appeared. The total distance walked in 6 minutes was recorded to the nearest decimetre. Standardised encouragements were provided at recommended intervals as per guideline instruction (American Thoracic Society, 2002). Supervision and measurement of the 6MWT was performed by one of four trained members (three physical therapists, one research nurse). In order to exclude any learning effects, the test was repeated within 3 days. The distance achieved on the second trial was included. With an intra class correlation of 0.96 [95% confidence interval (CI):0.94-0.98], the 6MWT has been shown to be a reliable test to assess the physical fitness in patients with schizophrenia (Vancampfort et al., 2011).

2.6. Physical activity assessment

The International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003) was completed to evaluate the level of physical activity participation. The IPAQ uses a structured format that asks participants to recall activities for each of the last seven preceding days in morning, afternoon, and evening time periods. On the basis of what activities participants self-reported, the interviewer also clarified the perceived intensity of that specific activity. A continuous indicator was calculated as a sum of weekly metabolic equivalent (MET)-minutes per week of physical activity. The MET energy expenditure was estimated by weighting the reported minutes per week by a MET energy expenditure estimate for each type of activity (low, moderate and vigorous intensity physical activity). MET-levels were obtained from Ainsworth et al. (2000). The weighted MET-minutes per week were calculated as duration x frequency per week x MET-intensity, which were then summed to produce a weighted estimate of total physical activity from all reported activities per week. Previous research

indicated that the IPAQ can be considered as a reliable surveillance tool to assess levels of PA in patients with schizophrenia (Faulkner et al., 2006; Soundy et al., 2014).

2.7. Psychiatric symptoms

Patients were assessed for psychiatric symptoms using the Psychosis evaluation tool for common use by caregivers (PECC) (De Hert et al., 1998). The semi-structured PECC-interview evaluates 100 symptom items on a 7-pointscale. Symptoms are grouped in 5 factors: positive, negative, depressive, cognitive and excitatory symptoms. In this study we only used the overall score. The total score ranges from 20 to 140 with higher scores indicating more severe psychopathology. Validation results (De Hert et al., 2002) suggest that the PECC can be successfully used for the evaluation of clinical symptoms in schizophrenia.

2.8. Antipsychotic medication use

Current antipsychotic medication use was recorded for each patient and converted into a daily equivalent dosage of chlorpromazine in accordance to the guidelines from Gardner et al. (2010).

2.9. Statistical analyses

Unpaired t tests with Bonferroni corrections for continuous variables and Fisher exact tests for categorical variables were used to examine differences in characteristics between patients with and without MetS and between patients with and without restrictive lung disease. All analyses were performed using SPSS (version 20.0). The study procedure was approved by the Scientific Committee of the UPC KU Leuven, Belgium. All participants gave their written informed consent.

3. Results

3.1. Patients' characteristics

Eighty patients with schizophrenia (55♂; 36.8 ± 10.0 years; age range=18-58years) were included. Twenty-eight patients with schizophrenia (35%) fulfilled the criteria for MetS according to the International Diabetes Federation criteria (Alberti et al., 2006). Three patients with schizophrenia had a FEV1/FVC<0.70 which is the major criterion for a chronic obstructive pulmonary disease (COPD), while 21 patients fulfilled the criteria for restrictive lung disease (FEV1-to-FVC ratio ≥ 0.70 and FVC <80% predicted) (Global Initiative for Chronic Obstructive Lung Disease, 2013).

3.2. Comparisons between patients with and without MetS

As shown in Table 1, schizophrenia patients with MetS have a significantly reduced predicted FVC and FEV1 compared with schizophrenia patients without MetS. Significantly more patients with MetS were diagnosed with restrictive lung dysfunction. In contrast, no differences in the prevalence of obstructive lung dysfunction was observed between patients with and without MetS. The FEV1-to-FVC ratio did also not differ between schizophrenia patients without and with MetS. Finally, patients with MetS were significantly less physically active and performed significantly worse on the 6MWT than those without MetS.

[Insert Table 1 about here]

3.3. Comparisons between patients with and without restrictive lung disease

Table 2 demonstrated that schizophrenia patients with restrictive lung disease had a significantly larger waist circumference than those without restrictive lung disease. No significant differences in other metabolic parameters were observed. Patients with restrictive

lung disease were also significantly less physically active and performed significantly worse on the 6MWT than those without restrictive lung disease.

[Insert Table 2 about here]

4. Discussion

4.1. General findings

To the best of our knowledge, this pilot study is the first to demonstrate that in patients with schizophrenia the presence of MetS is associated with an increased prevalence of restrictive lung dysfunction (diagnosed as FEV1-to-FVC ratio ≥ 0.70 and FVC $< 80\%$ predicted). While the presence of MetS (n=28; 35%) is in accordance with previous studies (Vancampfort et al., 2013a; Mitchell et al., 2013a & b), the prevalence of RLD (n=21; 26.2%) in our study is lower than the 48% reported by Aggarwal (2012). A possible reason might be the higher age range between studies, which was 23 to 74 years in the study by Aggarwal (2012) and 18 to 58 years in the present study. In contrast with an increased prevalence of RLD, the prevalence of COPD was not higher in the MetS group. The limited number of patients with COPD in our sample resulted in an insufficient power for detection of any association. Previous research in the general population (Ford & Mannino, 2004; Fimognari et al., 2007; Scarlata et al., 2013) showed that the restrictive, but not the obstructive respiratory pattern, is associated with MetS and insulin resistance, although data are conflicting (Lam et al., 2010) indicating that more research taking into account confounders such as smoking and physical activity is also needed here.

As the MetS is unlikely to be a homogeneous entity (Gale, 2008), we explored differences in each of its components between patients with and without restrictive lung function impairment. Only waist circumference differed significantly between patients with and without RLD. The current preliminary data indicates that abdominal obesity might be an

important determinant of the association between MetS and restrictive lung function impairment. Next to a possible mechanical obstacle to ventilation by visceral fat (Lessard et al., 2011), another reason might be that visceral fat produces pro-thrombotic and inflammatory mediators, including C-reactive protein, interleukin-6, and tumor necrosis factor-alpha (Ouchi et al., 2011).

However, there are other mechanisms independent of abdominal obesity by which MetS might affect lung function (Mannino et al., 2003b). For example, pathological microvascular changes may affect gas transfer across the alveolar-capillary membrane (Chance et al., 2008). In patients with schizophrenia metabolic changes may result in weakened aerobic and peripheral and respiratory muscular fitness while somatic pain associated with pre-diabetes is associated with a sedentary lifestyle, which in turn may contribute to an increased risk for pulmonary dysfunctions (Vancampfort et al., 2012; 2013c). Within this study we did not collate data on gas transfer or respiratory muscle dysfunction which would have enabled us to generate conclusions with greater certainty. The current data, in contrast, demonstrated that patients with RLD are less physically active and have a lower physical fitness than patients without RLD. Third, state and trait inflammatory markers associated with schizophrenia are known to be elevated independent from abdominal obesity (Manu et al., 2014). However, it is still unclear in which way these inflammatory changes may influence the expression of pulmonary dysfunctions in patients with schizophrenia.

4.2. Limitations

Although our current findings in patients with schizophrenia fit well with the recent documentation in the general population that the prevalence of MetS is associated with restrictive lung impairment (Ford & Mannino, 2004; Lin et al., 2006; Leone et al., 2009; Scarlata et al., 2013), the findings need to be interpreted with caution because of some

methodological limitations. First, the current pilot study had a small sample size making it difficult to generalize findings. Due to the limited number of patients with COPD we were not able to categorize these patients into classifications of mild, moderate or severe COPD. Second, the diagnosis of obstructive and restrictive patterns was made on the basis of low dynamic lung volumes while a definitive diagnosis of restrictive patterns would require the finding of decreased total lung capacity (Aaron et al., 1999). Therefore, it is possible that a few patients classified in the restrictive group had increased residual volume and, afterwards, normal total lung capacity. However, the GOLD-criteria have been found to have a high diagnostic accuracy versus a diagnosis of restrictive pattern based on total lung capacity measurement (Aaron et al., 1999). Third, the cross-sectional nature of our study means that it is impossible to infer causality or to specify the direction of effect. Fourth, we did not include parameters such as socio-economic status, educational level, duration of illness and treatment and smoking history in order to increase the external validity. Fifth, the reliance on self-reported recall physical activity is a method that is prone to both systematic and random errors (Soundy et al., 2007 & 2014).

4.3. Future research

Confirmatory prospective analyses in larger and well-defined samples are required to elucidate a causal pathway between lung function parameters and metabolic variables. In particular a confirmatory analysis in a drugs-naïve and smoking-free population is needed in order to avoid the confounding factor of antipsychotic treatment and smoking. Such studies need also accurate characterization of restrictive lung dysfunction, adiposity and possible confounders such as physical fitness and physical activity. In addition, research should acquire information on the measurement of the diffusing capacity of the lungs for carbon

monoxide, gas exchange parameters, inflammatory markers, respiratory muscle strength, plasmatic insulin and c-peptide levels.

In conclusion, our data suggest that in patients with schizophrenia the presence of MetS is associated with a restrictive lung dysfunction. Further prospective analyses to better elucidate the complex interrelationships between MetS and lung function parameters are highly needed.

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Table 1. Comparisons in baseline characteristics between patients with schizophrenia with and without metabolic syndrome

Variables	Schizophrenia with MetS (n=28)	Schizophrenia without MetS (n=52)	P
Gender (M/F)	18/10	37/15	0.61
Age (years)	38.2±2.8	36.0±10.6	0.36
BMI (kg/m ²)	29.8±6.2	24.4±3.4	<0.001*
Smoking (cig/day)	17.9±15.0	13.1±14.5	0.18
6MWT (m)	491.3±75.3	633.2±92.1	<0.001*
IPAQ (total MET-min/week)	709.3±675.3	1604.3±1307.7	<0.001*
PECC total	46.4±13.9	40.3±12.4	0.06
Chlorpromazine eq (mg/day)	828.5±492.0	612.4±333.8	0.04
FVC (% predicted)	75.3±11.1	85.4±11.4	<0.001*
FEV1 (% predicted)	77.4±13.2	87.3±12.1	<0.001*
FEV1/FVC (%)	0.80±0.12	0.83±0.09	0.27
Respiratory health			
COPD (%)	2 (7.1%)	1 (1.9%)	0.28
RLD (%)	13 (46.4%)	8 (15.4%)	<0.001*

Data expressed as mean ± standard deviation, unpaired t-tests with Bonferroni corrections (*significant when $p < 0.006$) for continuous variables and Fisher Exact tests for differences in gender distribution ($p < 0.05$), MetS= metabolic syndrome, BMI = body mass index, FVC= forced vital capacity, FEV1=forced expiratory volume for 1 second, 6MWT= 6-minute walk test, IPAQ= International Physical Activity Questionnaire, MET= metabolic equivalent, PECC= psychosis evaluation tool for common use by caregivers, eq= equivalents, COPD=chronic obstructive pulmonary disease, RLD= restrictive lung disease.

Table 2. Comparisons in baseline characteristics between patients with schizophrenia with and without restrictive lung disease

Variables	Schizophrenia with RLD (n=21)	Schizophrenia without RLD (n=59)	<i>P</i>
Gender (M/F)	18/3	37/22	0.06
Age (years)	37.9±9.6	35.0±10.1	0.25
BMI (kg/m ²)	29.0±7.2	25.3±4.4	0.04
Smoking ^o (cig/day)	19.9±15.1	13.0±14.3	0.08
6MWT (m)	502.6±92.3	612.4±101.2	<0.001*
IPAQ (total MET-min/week)	653.6±777.9	1517.9±1248.7	0.001*
PECC total	44.9±12.2	41.6±12.0	0.41
Chlorpromazine eq (mg/day)	874.5±564.9	617.1±315.8	0.06
Waist circumference (cm)	90.7±12.5	105.6±14.7	0.003*
Systolic blood pressure (mmHg)	120.1±14.1	122.3±11.6	0.61
Diastolic blood pressure (mmHg)	80.6±10.7	77.1±8.9	0.27
Triglycerides (mg/dl)	140.5±83.3	127.7±71.8	0.61
High density lipoproteins (mg/dl)	59.3±28.9	52.8±15.3	0.42
Fasting glucose (mg/dl)	89.2±14.5	85.8±10.2	0.42

Data expressed as mean ± standard deviation, unpaired t-tests with Bonferroni corrections (* significant when $p < 0.0038$) for continuous variables and Fisher Exact tests for differences in gender distribution ($p < 0.05$), MetS= metabolic syndrome, BMI = body mass index, 6MWT= 6-minute walk test, IPAQ= International Physical Activity Questionnaire, MET= metabolic equivalent, PECC= Psychosis evaluation tool for common use by caregivers, eq= equivalents, COPD=chronic obstructive pulmonary disease, RLD= restrictive lung disease.